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Rosemarie R. Wilk-Orescan, Esq.	Rosemarie R Wilk Orescan	March 9, 2001
Type or print name	Signature	Date

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicant(s): Rosok, et al.
Serial No.: 08/905,293
Filed: August 1, 1997
Art Unit: 1641
Examiner: S. Devi
Attorney Docket No.: ON-0146A

Title: Method for Inhibiting Immunoglobulin-Induced Toxicity Resulting From the Use of Immunoglobulins in Therapy and In Vivo Diagnosis

Assistant Commissioner for Patents
Washington, D.C. 20231

APPELLANTS' BRIEF UNDER 37 CFR §1.192

Sir:

Enclosed is Appellants' corrected brief (in triplicate) filed in response to the Notification of Non-Compliance with 37 CFR §1.192(c) mailed February 12, 2001, having a response time limit of one month.

Appellants reserve the right to request an Oral Hearing in accordance with 37 CFR §1.194 following receipt of the Examiner's response.

The Commissioner is hereby authorized to charge any additional fees under 37 CFR §1.17, which may be required, or credit any overpayment, to Account No. 19-3880 in the name of Bristol-Myers Squibb Company.

Respectfully submitted,

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Date: March 9, 2001

I. Real Party in Interest

Applicants Mae Joanne Rosok and Dale E. Yelton filed this application on August 1, 1997, and assigned their rights to Bristol-Myers Squibb Company, said Assignment was recorded on February 23, 1998, at Reel 8973, Frame 0208.

II. Related Appeals and Interferences

Appellants, Appellants' legal representatives and the Assignee of the present Application are not aware of any other appeals or interferences that will directly affect or be directly affected by or have bearing on the Board's decision in the pending appeal.

III. Status of Claims

Claims 1-52 are pending. Claims 1-22 and 28-31 are under examination, and are the subject of the current appeal. Claims 23-27 and 32-52 are withdrawn from consideration without prejudice to subsequent renewal. A copy of the appealed claims is attached hereto as Appendix A.

The claims on appeal currently stand rejected under 35 U.S.C. §102(b), and under 35 U.S.C. §103(a).

IV. Status of Amendments

No amendments were filed subsequent to final rejection. In an Advisory Action dated April 10, 2000, the Examiner indicated that all pending claims 1-22 and 28-31 remained rejected under 35 U.S.C. §102(b), and under 35 U.S.C. §103(a).

V. Summary of Invention

The present invention relates to methods for inhibiting or reducing immunoglobulin-induced toxicity resulting from therapy or *in vivo* diagnosis.

A. Background

Immunoglobulin (Ig) molecules which constitute an important part of the immune system are of great interest because they (1) react with a diverse family of ligands, (2) possess different effector functions and (3) are of great biological importance. Despite its potential, a persistent problem with immunoglobulin therapy has been, among other problems, the toxic effect to normal cells of using antibodies which recognize both normal and diseased cells. This problem is far-reaching because the majority of antibodies presently available recognize a target

located on both normal and diseased cells. (Specification page 1 lines 28-31; page 2 lines 1-4).

Generally, whole antibody molecules are composed of the heavy (H) and two light (L) chains which are held together by covalent (disulfide) and non-covalent interactions. Each chain contains a variable region (V) and a constant region (C). The variable regions at the amino termini of the two chains form the antigen binding region. The constant region of the H chain has three components or domains. Occasionally, the first constant region domain (CH_1) interacts with the C region of the L chain through hydrophobic interactions and generally a disulfide bond, depending on isotype. The next C region stretch is the hinge-acting disulfide bond stably introduced between two H chains. The second constant domain (CH_2) is adjacent to the hinge region. CH_2 contains sequences important for effector functions of the antibody, such as the sequences responsible for complement fixation, and Fc receptor binding. The third constant region (CH_3) is located at the carboxyl terminus of the H chain, and is considered to play an important role in H chain assembly as well as some C region functions. (Specification page 2, lines 23-29; page 3 lines 1-7).

Today many antibodies in clinical trials are directed against tumor associated antigens. Most tumor associated antigens are not tumor specific but are also generally found on the cell surface of some normal, non-tumorigenic cells. The clinical use of some antibodies directed against tumor associated antigens are limited because of the toxicity associated with their use. (Specification page 3, lines 9-13).

B. Claimed Invention

The present invention provides methods for inhibiting immunoglobulin-induced toxicity by using known immunoglobulin or Ig fusion protein molecules which are structurally altered in their constant regions so that the resulting structurally altered immunoglobulin or Ig fusion protein molecules exhibit reduced or inhibited toxicity *in vivo* compared to their original unmodified counterparts. As there appears to be at least two toxicity associated domains in the immunoglobulin molecule, one roughly localized to amino acids 231-238 and another roughly localized to amino acids 310-331, an example of the structural alteration of multiple toxicity associated domains comprises the insertion, substitution or deletion of amino acid residues in both of these domains. This

definition excludes structural alterations targeting a single toxicity associated domain. Inhibiting immunoglobulin-induced toxicity means to reduce or alleviate symptoms generally associated with toxicity caused by immunoglobulin or Ig fusion protein therapy. (Specification page 3, lines 27-29, page 4 lines 1-2, page 9, lines 5-7, page 10, lines 8-15).

In accordance with the practice of the invention, structural alteration of the constant region is effected by deletion of the entire constant region, by deletion of the CH_2 domain, by deletion of the portion of the CH_2 domain that binds the Fc receptor, by deletion of that portion of the CH_2 domain that binds the complement component Clq, or multiple deletions in discrete Fc receptor and complement component binding domains. Alternatively, structural alternation is effected by single or multiple mutations in the CH_2 domain such as amino acid insertions and substitutions. Multiple amino acids in a single toxicity associated domain in the constant region can be altered as well. Structural alteration can also be effected by isotype switching (also known as class switching) so that the altered molecule does not induce toxicity in the subject. (Specification page 4, lines 7-24, page 11, lines 14-20).

Following the present invention, one can select a target, generally the target is associated with the disease and the antibody directed to the target is known. The constant region of the antibody so selected is then structurally altered so that the immunoglobulin-induced toxicity is inhibited. The structurally altered antibody is then administered to the subject under conditions that the structurally altered antibody recognizes and binds the target and that such binding directly or indirectly alleviates symptoms associated with the disease. (Specification page 16, lines 25-27, page 17, lines 1-2, lines 7-10).

The present invention also provides structurally altered BR96 or BR96 Ig fusion proteins. Structurally altered BR96 antibodies or Ig fusion proteins have the variable region of BR96 and a modified constant region. This modification provides structurally altered BR96 antibodies or Ig fusion proteins with the ability to inhibit immunoglobulin-induced toxicity. (Specification page 21, lines 6-10).

There is a need for methods for inhibiting toxicity associated with immunoglobulin use in the field of disease therapy and in *in vivo* diagnosis. Applicants addressed this need by discovering methods for inhibiting or reducing toxicity to normal cells generally associated with immunoglobulin immunotherapy or *in vivo* diagnosis, wherein the immunoglobulin recognizes both diseased and

normal cells. Applicants' discovery involves generating immunoglobulin molecules or Ig fusion proteins having structurally altered constant regions which inhibit or reduce immunoglobulin-induced toxicity.

VI. Issues

Is each of claims 1, 2, 5 and 7-10 unpatentable under 35 U.S.C.§102(b) as anticipated by Morgan et al. (WO 94/29351)?

Is each of claims 3, 4, 6 and 11-22 unpatentable under 35 U.S.C.§103(a) as obvious over Morgan et al. (WO 94/29351) as applied to claim 1 or 2, and in view of Yelton et al. (U.S. Patent No. 5,792,456) or Muroi et al. (Blood 79: 713-719, 1992), and Gilles et al. (Human Antibodies and Hybridomas 1: 47-54, 1990)?

Is each of claims 28-31 unpatentable under 35 U.S.C.§103(a) as obvious over Morgan et al. (WO 94/29351) in view of Yelton et al. (U.S. Patent No. 5,792,456)?

as applied ...

VII. Grouping of Claims

The claims stand or fall together for each ground of rejection which appellant contests for the sole purpose of allowing the Board to select a single claim from each group for review, and to decide the appeal as to the ground of rejection on the basis of that claim alone.

VIII. Argument

A. Rejection under 35 U.S.C.§102(b). Is each of claims 1, 2, 5 and 7-10 unpatentable under 35 U.S.C.§102(b) as anticipated by Morgan et al. (WO 94/29351)?

The Examiner has maintained the rejection of claims 1, 2, 5 and 7-10 under 35 U.S.C.§102(b) as anticipated by Morgan et al. (WO 94/29351).

A claim is anticipated only if each and every element, as set forth in the claim, is found in a single prior art reference. Verdegaal Bros. v. Union Oil Co. of California, 2 USPQ 2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the...claim." Richardson v. Suzuki Motor Co., 9 USPQ 2d 1913, 1920 (Fed. Cir. 1989).

The claimed invention is directed to methods for inhibiting immunoglobulin-induced toxicity resulting from immunoglobulin immunotherapy in a subject. In this context Applicants disclose the use of antibodies having alterations in **multiple toxicity associated domains** so that the antibodies are no longer able to (1) mediate the antibody

dependent cellular cytotoxicity response or (2) activate complement. Moreover, Applicants establish that antibodies having alterations in multiple toxicity associated domains have a reduced toxicity *in vivo*.

At page 10, lines 8-15, Applicants discuss the definition of "multiple toxicity associated domains" where they teach: *[A]s used herein the terms "multiple toxicity associated domains" means more than one discrete toxicity associated domain. As there appear to be at least two toxicity associated domains in the immunoglobulin molecule, one roughly localized to amino acids 231-238 and another roughly localized to amino acids 310-331, an example of the structural alteration of multiple toxicity associated domains comprises the insertion, substitution or deletion of amino acid residues in both of these domains.* ***This definition excludes structural alterations targeting a single toxicity associated domain.***

By utilizing antibodies which have alterations both in a toxicity associated domain in the C-terminal region of the CH_2 domain (roughly localized to amino acids 310-331) as well as alterations in a toxicity associated domain in the N-terminal region of the CH_2 domain (roughly localized to amino acids 231-238), Applicants provide a means of significantly inhibiting immunoglobulin-induced toxicity.

Morgan et al. (WO 94/29351) disclose methods which utilize antibodies where amino acid residues in the N-terminal domain of the CH_2 region are altered so that the ability of the antibody to fix complement and bind FcR is altered as compared to unaltered antibody (see i.e. page 5, lines 11-1). In delineating this portion within the N-terminal domain of the CH_2 region that is altered in their methods, Morgan et al., teach at page 4, lines 4-7: *[W]e have found that the amino acid residues necessary for Clq and FcR binding of human IgG1 are located in the N-terminal region of the CH2 domain, residues 231 to 238, using a matched set of engineered antibodies based on the anti-HLA DR antibody L243.*

Morgan et al. do not teach or suggest the use of antibodies having alterations in multiple toxicity associated domains.

As illustrated above, Morgan et al. teach methods utilizing antibodies having alterations in a **single** toxicity associated domain and fail to teach or suggest antibodies having alterations in multiple toxicity associated domains. In addition, while Morgan et al. utilize antibodies having mutations in the C-terminal domain of CH_2 in assays which evaluate the antibodies of their invention they teach that it is the alterations in the **N-terminal region** of CH_2 that reduce toxicity. In particular, Morgan et al. direct the skilled artisan to target residues in amino acid positions 231-238 because of their fundamental

role in complement activation (see i.e. page 4, line 4-7). Moreover, Morgan et al. specifically question the biological significance of other amino acid residues within the CH_2 region, noting that residues 318, 320 and 322 in the C-terminal domain, while possibly being involved in the complement cascade, are not sufficient for complement activation (see i.e. page 4, line 5).

In addition to failing to teach or suggest antibodies having alterations in multiple toxicity domains, Morgan et al. cannot anticipate Applicants' methods for inhibiting immunoglobulin-induced toxicity because this reference provides no data on immunoglobulin-induced toxicity resulting from immunoglobulin immunotherapy. In particular, while Morgan et al. disclose experiments showing how alterations in the N-terminal region of CH_2 effect the ability of antibodies to fix complement or mediate antibody dependent cellular toxicity *in vitro*, they provide no data on actually inhibiting immunoglobulin-induced toxicity. Moreover, Morgan et al. fail to provide any information on which of the multiple toxicity associated domains in CH_2 control immunoglobulin-induced toxicity. For this reason one skilled in the art cannot determine which alterations in CH_2 are associated with a reduction in immunoglobulin-induced toxicity. In contrast, Applicants' *in vivo* data clearly shows that alterations in multiple toxicity associated domains in the constant region inhibit immunoglobulin-induced toxicity that results from immunotherapy (see i.e. Example 3).

As Morgan et al. fail to either teach or suggest methods for inhibiting immunoglobulin-induced toxicity by using antibodies having modifications in multiple toxicity associated domains or provide any insight on which alterations in CH_2, if any, are associated with a reduction in immunoglobulin-induced toxicity, this reference cannot anticipate the claimed invention.

B. Rejection under 35 U.S.C.§103(a). Is each of claims 3, 4, 6 and 11-22 unpatentable under 35 U.S.C.§103(a) as obvious over Morgan et al. (WO 94/29351) as applied to claim 1 or 2, and in view of Yelton et al. (U.S. Patent No. 5,792,456) or Muroi et al. (Blood 79: 713-719, 1992), and Gilles et al. (Human Antibodies and Hybridomas 1: 47-54, 1990)?

The Examiner has maintained the rejection of claims 3, 4, 6 and 11-22 under 35 U.S.C.§103(a) as obvious over Morgan et al. (WO 94/29351) as applied to claim 1 or 2,

and in view of Yelton et al. (U.S. Patent No. 5,792,456) or Muroi et al. (Blood 79: 713-719, 1992) and Gilles et al. (Human Antibodies and Hybridomas 1: 47-54, 1990).

In order to render the instant claims obvious, in view of the cited references, there must be some suggestion, found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, for combining the references. In re Jones, 21 USPQ 2d 1941, 1943-44 (Fed. Cir. 1992). Conspicuously missing from the record in this case is any evidence, other than the Examiner's speculation, that one skilled in the art would have been motivated to combine the cited references, and that such combination would successfully yield Applicants' invention. See Jones, at 1944.

As illustrated above, Morgan et al. do not teach or suggest methods for inhibiting immunoglobulin-induced toxicity by using antibodies having modifications in multiple toxicity associated domains. The deficiencies in Morgan et al. are not remedied by the teachings of Gilles et al., Yelton et al or Muroi et al.

While Gilles et al. provide a method for mutating the constant region of human gamma chain and note that these mutants exhibit little antibody dependent cell mediated cytotoxicity (ADCC) activity or complement dependent cytotoxicity (CDC) activity, a combination of this reference with Morgan et al. does not teach that antibodies having alterations in multiple toxicity associated domains can be used in methods for inhibiting immunoglobulin-induced toxicity. Moreover, because the biological significance of the amino acid residues in the C-terminal domain is disparaged in Morgan et al., one skilled in the art would be disinclined to combine these references in the manner suggested by the Examiner. In addition, even if one was to try to combine such disparate references, the resulting combination would not generate the claimed invention. Therefore, the claimed invention cannot be obvious in light of these references.

While Yelton et al. provide teachings about mutant BR96 as a composition of matter and its use in some contexts, this reference does not disclose Applicants' claimed methods for inhibiting immunoglobulin-induced toxicity. In particular, while Yelton et al. note that functional equivalents of mutant BR96 antibody which do not include the Fc region do not exhibit ADCC or CDC properties, a combination of this reference with Morgan et al. does not teach that antibodies having alterations in multiple toxicity associated domains can be used in methods for inhibiting immunoglobulin-induced toxicity. Moreover, because the biological significance of the amino acid residues in the C-terminal domain is disparaged in Morgan et al., one skilled in the art would be disinclined to combine these teachings in the manner suggested by the Examiner. In particular, even if one was to try to combine such disparate references, the resulting

combination would not generate the claimed invention. Therefore the claimed invention cannot be obvious in light of these references.

Muroi et al. simply disclose antibodies that recognize and bind to Le^x. This reference does not overcome the deficiencies in the other reference cited by the Examiner and a combination of these references does not teach or suggest that antibodies having alterations in multiple toxicity associated domains can be used in methods for inhibiting immunoglobulin-induced toxicity.

C. Rejection under 35 U.S.C.§103(a). Is each of claims 28-31 unpatentable under 35 U.S.C.§103(a) as obvious over Morgan et al. (WO 94/29351) in view of Yelton et al. (U.S. Patent No. 5,792,456)?

The Examiner has maintained the rejection of claims 28-31 under 35 U.S.C.§103(a) as obvious over Morgan et al. (WO 94/29351) in view of Yelton et al. (U.S. Patent No. 5,792,456).

Applicants point out that Morgan et al. do not teach or suggest methods for inhibiting immunoglobulin-induced toxicity by using antibodies having modifications in multiple toxicity associated domains. As illustrated above, this deficiency in Morgan et al. is not remedied by the teachings of Yelton et al.

Because the references cited by the Examiner fail to contain some suggestion, either explicit or implicit, of the combination proposed by the Examiner, obviousness cannot be established. In re Bell, 26 USPQ 2d 1529, 1531 (Fed. Cir. 1993). (Obviousness "cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination."). Moreover, lacking from each and every reference, taken alone or in combination, is the necessary claim element of alterations in **multiple** toxicity associated domains of an immunoglobulin molecule. It is impossible for the claims to be rendered obvious when all of the claimed elements are not present in the references. Since the references cited by the Examiner fail to teach or suggest the limitations of the pending claims, obviousness cannot be established. Motorola Inc. v. Interdigital Technology Corp., 43 USPQ 2d 1481, 1490 (Fed. Cir. 1997) (Federal Circuit reversed an obviousness determination because "no combination of prior art references for obviousness describes the four particular functions recited in the claim...).

D. Conclusion

In review, the claims of the present application were improperly rejected under 35 U.S.C. §§102(b) and 103(a) for the reasons outlined herein. The Board is respectfully requested to reverse the appealed decision of the Examiner.

Respectfully submitted,

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IX. Appendix A

Appealed Claims

1. A method for inhibiting immunoglobulin-induced toxicity resulting from immunoglobulin immunotherapy in a subject comprising administering an immunoglobulin molecule to the subject, the immunoglobulin molecule having a variable region and a constant region, the immunoglobulin molecule being modified prior to administration by structurally altering multiple toxicity associated domains in the constant region so that immunoglobulin-induced toxicity is inhibited.

2. A method for inhibiting immunoglobulin-induced toxicity resulting from immunoglobulin immunotherapy in a subject comprising administering a structurally altered antibody to the subject, the structurally altered antibody comprising a variable region and a constant region, multiple toxicity associated domains in the constant region being modified so as to render the constant region unable to mediate an antibody dependent cellular cytotoxicity response or activate complement thereby inhibiting immunoglobulin-induced toxicity resulting from immunotherapy.

3. A method for inhibiting immunoglobulin-induced toxicity resulting from immunotherapy in a subject comprising administering an Ig fusion protein to the subject, the Ig fusion protein having multiple structurally altered toxicity associated domains in the constant region.

4. A method for inhibiting immunoglobulin-induced toxicity resulting from immunotherapy in a subject comprising administering an Ig fusion protein to the subject, the Ig fusion protein comprising a modified constant region, the modification being a structural alteration in multiple toxicity associated regions within the CH_2 domain.

5. A method for preventing immunoglobulin-induced toxicity resulting from immunotherapy for a disease in a subject comprising:

   (a) selecting an immunoglobulin which recognizes and binds a target, the target being associated with the disease;

   (b) mutating the immunoglobulin so selected by structurally altering multiple toxicity associated domains in the constant region of the immunoglobulin thereby creating a structurally altered immunoglobulin;

(c) administering the structurally altered immunoglobulin of step (b) to the subject under conditions so that the structurally altered immunoglobulin recognizes and binds the target thereby alleviating symptoms associated with the disease, the structural alteration of the constant region thereby preventing immunoglobulin-induced toxicity in the subject.

6. A method for preventing immunoglobulin-induced toxicity resulting from immunotherapy for a disease in a subject comprising:

(a) selecting an Ig fusion protein which recognizes and binds a target, the target being associated with the disease;

(b) structurally altering multiple toxicity associated domains in the CH_2 domain of the constant region of the Ig protein so selected;

(c) administering the structurally altered Ig fusion protein of step (b) to the subject under conditions so that the structurally altered Ig fusion protein recognizes and binds the target thereby alleviating symptoms associated with the disease, the structural alteration of the CH_2 domain thereby preventing immunoglobulin-induced toxicity in the subject.

7. The method of claim 1, 2, 3, 4, 5, or 6, wherein the portion of the constant region is the CH_2 domain.

8. The method of claim 1 or 5, wherein the immunoglobulin molecule is IgG.

9. The method of claim 1 or 5, wherein the immunoglobulin molecule is IgM.

10. The method of claim 1 or 5, wherein the immunoglobulin molecule is IgA.

11. The method of claim 2, wherein the antibody recognizes and binds Le^y.

12. The method of claim 2, wherein the antibody recognizes and binds to Le^x.

13. The method of claim 2, wherein the antibody is a monoclonal antibody BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.

14. The method of claim 2, wherein the antibody is a chimeric antibody ChiBR96 produced by the hybridoma HB 10460 as deposited with the ATCC.

15. The method of claim 1 or 5, wherein the immunoglobulin recognizes and binds Le^y.

16. The method of claim 1 or 5, wherein the immunoglobulin recognizes and binds to Le^x.

17. The method of claim 1 or 5, wherein the immunoglobulin is a monoclonal antibody BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.

18. The method of claim 1 or 5, wherein the immunoglobulin is a chimeric antibody ChiBR96 produced by the hybridoma HB 10460 as deposited with the ATCC.

19. The method of claim 3, 4, or 6, wherein the Ig fusion protein recognizes and binds Le^y.

20. The method of claim 3, 4, or 6, wherein the Ig fusion protein recognizes and binds to Le^x.

21. The method of claim 3, 4, or 6, wherein the Ig fusion protein comprises the antigen binding site of monoclonal antibody BR96 produced by the hybridoma HB 10036 as deposited with the ATCC.

22. The method of claim 3, 4, or 6, wherein the Ig fusion protein comprises the antigen binding site of chimeric antibody ChiBR96 produced by HB 10460 as deposited with the ATCC.

28. The method of claim 2, wherein the antibody is conjugated to a cytotoxic agent.

29. The method of claim 1 or 5, wherein the immunoglobulin is conjugated to a cytotoxic agent.

30. The method of claim 3, 4, or 6, wherein the Ig fusion protein is conjugated to a cytotoxic agent.

31. The method of claim 28, wherein the cytotoxic agent is selected from the group consisting of antimetabolites, alkylating agents, anthracyclines, antibiotics, anti-mitotic agents, and chemotherapeutic agents.